

# United States and Canadian Academy of Pathology

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## PLATFORM and POSTER PRESENTATIONS

### Autopsy

#### 1 Primary and Immediate Causes of Death in Obese Versus Nonobese Hospital Patients

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**Background:** Obesity is an increasingly prevalent condition in the United States that has been linked to numerous secondary health conditions. Although some believe that obesity is associated with an enhanced risk of early death, causes of death in obese patients have received relatively little investigation. This study was performed to compare primary causes of death (PCODs) and immediate causes of death (ICODs) in obese and nonobese hospital patients.

**Design:** Reports from 108 adult autopsies performed during 2003 and 2004 in a major teaching hospital were reviewed. For each patient, the body mass index (BMI) was calculated. Obesity was defined by a BMI $\geq$ 30 kg/m<sup>2</sup>, and subjects with a BMI $<$ 30 were considered nonobese. According to these criteria, 40 patients were obese and 68 patients were nonobese. The PCOD and ICOD were determined for each patient, and the frequencies of the major diagnostic categories of PCODs and ICODs were compared for the obese and nonobese patient groups.

**Results:** Arteriosclerotic cardiovascular disease was the most common PCOD in obese and nonobese patients, with a frequency of 37.5% in both groups. This was followed by malignancy (obese-17.5%, nonobese-8.8%); infection (obese-12.5%, nonobese-8.8%); and diabetes mellitus (both groups-7.5%). The most common ICOD for obese and nonobese patients was infection (obese-35.0%, nonobese-40.0%). In obese patients, this was followed by intracranial hemorrhage (22.5%) and arteriosclerotic and thrombotic cardiovascular disease (20.0%). In nonobese patients, the second most common ICOD was arteriosclerotic and thrombotic cardiovascular disease (23.5%), followed by intracranial hemorrhage (13.2%). Pulmonary embolism ranked fourth among the ICODs in obese patients, with a frequency of 12.5%, versus a frequency of 1.5% as an ICOD in nonobese patients.

**Conclusions:** In our series, the PCODs and ICODs in obese and nonobese patients were generally similar, with the exception of a substantially higher frequency of pulmonary embolism as an ICOD in the obese patient group. Interventions directed towards reducing the incidence of pulmonary embolism may be especially important for obese hospitalized patients.

#### 2 An Analysis of the Findings at Autopsy in 663 Normal, Overweight, Obese and Morbidly Obese Patients

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**Background:** Co-morbid conditions are associated with obesity such as hypertension (HT), diabetes mellitus (DM), and cancer and a decrease in life span. The autopsy is an important mechanism to determine the accurate cause of death, thus a study was undertaken of 663 autopsies comparing the findings in normal and obese patients.

**Design:** The study included 663 consecutive permission autopsies performed at the University of Chicago between 1997-2003. The sample included those 19 years and older for whom height and weight were available. There were four groups based on BMI: 201 were normal (N), 187 overweight (OW), 196 obese (O) and 79 morbidly obese (MO). Demographic factors (age, sex, race), presence or absence of HT, DM, cancer, peripheral vascular disease (PVD), osteoarthritis (OA), end stage renal disease (ESRD), stroke and asthma were determined. Severity of coronary artery atherosclerosis (CAA), presence of CABG, severity of aortic atherosclerosis (AA) and presence of myocardial infarction (MI) were examined. CAA was divided into mild/moderate if  $<$ 75% stenosed and severe if  $>$ 75% stenosed. AA was graded from I-VII with I-V regarded as mild/moderate and  $>$ V as severe. Presence of MI was divided into 3 groups: acute MI, acute/old MI, and old MI.

**Results:** Overall difference in age at death between (N) and (MO) is statistically significant ( $p<.02$ ). Despite the younger age at death in the (MO) group, 42% in this group died after age 60. HT, DM, OA and asthma are statistically significantly increased in the (MO) group but PVD, ESRD or stroke is not increased in any group. Endometrial and colon cancers are statistically increased in the (MO) group, but all other cancers show no significant increase. There is no increase in incidence of CABG, CAA of mild/moderate and severe degree and AA of severe degree. There is a statistical increase in

incidence of mild AA in the (MO) group. There is no significant relationship between weight class and any type of MI.

**Conclusions:** A study of findings in 663 consecutive autopsies based on BMI revealed that some risk factors associated with obesity, such as HT, DM, OA and asthma are statistically significantly increased in the (MO) group as are endometrial and colon cancers. The incidence of severe CAA, AA, CABG, ESRD, stroke and any type of MI is not increased in any group. This would indicate that notwithstanding an increase in co-morbidities in (MO) other life threatening conditions such as MI and CAA are not significantly increased in the (MO) and (O) groups.

#### 3 Correlation between Prenatal Ultrasound and Fetal Autopsy Findings in Fetal Anomalies Terminated in the Second Trimester: A Preliminary Report

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**Background:** Comparison of major/minor anomaly findings in fetal autopsies evaluated following the termination of pregnancies based on major fetal anomalies detected by prenatal ultrasound examination in the second trimester.

**Design:** In a 28 month-long prospective study fetal autopsy results of 60 cases with major and minor anomalies were analyzed. Anomalies that prevent postpartum survival or require major surgery such as neural tube defect, limb absence, abdominal wall defect, and double exit right ventricle in heart were taken as major anomaly criteria. Cosmetic anomalies that do not affect postpartum survival such as polydactyl were accepted as minor anomaly criteria. In cases with major anomalies prior to fetal viability ( $<$  24 gestational weeks) or lethal anomalies, parents were informed about the situation and termination of pregnancy was recommended. Prior to the termination of pregnancy, 30 fetal materials were taken by amniocentesis or chorocentesis for cytogenetic analysis.

**Results:** Of the 60 cases with major fetal anomalies diagnosed by prenatal ultrasound examination, 50% had central nervous system anomaly, 18% had kidney and urinary tract anomaly, 10% had congenital heart disease, 7% had Meckel Gruber Syndrome, 3% had nonimmun hidrops, 3% had limb anomaly. All of these major anomalies were confirmed by fetal autopsy (100 % success rate in major anomalies). Success rate in prenatal ultrasonography for major + minor anomalies was determined as 76%. The percentage of additional minor anomalies detected in fetal autopsies were 19%. Five percent (5%) of the minor anomalies detected by prenatal ultrasonography could not be confirmed during autopsy. In 30 of the 60 cases, chromosome analysis was performed. In 7 (23%) of these cases number and structure anomaly was detected.

**Conclusions:** Evaluation of fetal autopsies following the termination of pregnancies based on major fetal anomalies detected by prenatal ultrasound examination enables diagnosis of additional pathologies, leading to better preconceptional consultation for the subsequent pregnancies.

Major fetal anomalies and accompanying other system findings based on prenatal ultrasound and post-mortem examination

Organ/anomaly	n	%
Central nerve system anomalies	30	50%
Congenital heart disease	6	10%
Kidney/urinary tract anomalies	11	19%
Meckel Gruber syndrome	4	7%
Others	9	14%
Total	60	100%

#### 4 Atrial Involvement in Acute Myocardial Infarction (AMI). An Autopsy Study of 100 Cases

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**Background:** Atrial involvement remains not diagnosed in most AMI autopsies. Its real frequency has been underestimated due to current autopsy protocols, which usually focus on ventricles and do not analyze atria in depth. The aim of this study is to define the atrial participation in a series of conventional transmural AMIs.

**Design:** A total of 100 consecutive patients who died of AMI at the coronary Care Unit were analyzed. All the cases had more than 18 hours of clinical evolution. At autopsy, both coronary arteries were filled up with barium gelatin solution for radiological studies. Main trunks were sectioned every 3 mm. Both atria were sliced just above the coronary sinus, and 1 cm above. The respective complete myocardial surfaces were histologically analyzed.

**Results:** Atria were involved in 66 cases [right, 50 (75.75%); left, 39 (59.09%); both, 26 (39.39%); septum, 19 (28.78%); atrium appendage, 6 (9.09%)]. Table shows coronary thrombosis and atrial AMI distribution.

CAT (n)	aAMI (n/%)	CAT (n)	aAMI (n/%)
RCA (47 cases)	39/82.98%		
LCX (13 cases)	10/76.92%	65 cases (RCA/LDX/DCO)	54/83.08%
DCO (5 cases)	5/100%		
LDA (35 cases)	12/34.28%	35 cases (LDA)	12/34.28%

CAT: coronary artery thrombosis, aAMI: atrial acute myocardial infarction, RCA: right coronary artery, LCX left circumflex, DCO: double coronary occlusion, LDA: left descending artery

**Conclusions:** The frequency and location of atrial involvement in AMI greatly depends on AMI type and on the occluded coronary artery. The obstruction of vessels running along the atrio-ventricular sulcus (RCA & LCX) develops atrial AMI twofold more frequently than LDA occlusion does.

## 5 Vascular Anatomy of the Atria. An Autopsy Study Helping To Understand the Atrial Acute Myocardial Infarction (aAMI)

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**Background:** Atrial vascular distribution is poorly known by most pathologists. The aim of this study is to review the atrial vascular supply and to give diagnostic keys to predict the topographic distribution of acute myocardial infarctions (AMI) in this location.

**Design:** Two complete slices of right and left atria were studied in 100 AMIs, 66 of them showing atrial participation. All cases were studied following the same protocol: the coronary tree was filled up with a barium gelatin solution allowing the X-ray study of the fine atrial coronary branches. Atrial slices were obtained just above the coronary sinus, and 1 cm above.

**Results:** The most common atrial arterial supply is as follows: The right atrium (RA) is almost entirely irrigated by branches of the right coronary artery (RCA), while the left atrium (LA) supply comes mainly from the left circumflex artery (LCX). The septum and the proximal anterior and posterior areas of both atria are also irrigated by branches of the RCA and LCX. RCA occlusion mainly affects RA (74.5%), while LCX obstruction involves LA (61.5%). Although LDA runs down to the ventricles, its occlusion damages atrial myocardium in a high percentage of cases (34.3%). The varied distribution of the sinus artery shows a correlation between sinus artery occlusion and sinus node necrosis (10/11).

CAT (n)	aAMI pres (n/%)	RA (n/%)	LA (n/%)	Septum (n/%)	aAMI abs (n/%)
RCA (47)	39/82.98%	35/74.47%	19/40.43%	10/21.28%	8/17.02%
LCX (13)	10/76.92%	5/38.46%	8/61.54%	4/30.77%	3/23.08%
LDA (35)	12/34.29%	6/17.14%	9/25.71%	2/5.71%	23/65.71%
DCO (5)	5/100%	3/60%	5/100%	3/60%	0/0%

CAT: coronary artery thrombosis, RA: right atrium, LA: left atrium, aAMI: atrial acute myocardial infarction, RCA: right coronary artery, LCX: left circumflex, LDA: left descending artery, DCO: double coronary occlusion.

**Conclusions:** Atria are involved in a high number of AMIs. Contrary to what happens in ventricular infarction, aAMI correlates with coronary distribution along the atrioventricular sulcus. RCA occlusion leads to posterior left ventricular infarction, while in the atria generates mainly right aAMIs. LCX occlusion is associated to left aAMIs. Surprisingly, LDA occlusion results in a relative high percentage of aAMIs, mainly located in LA.

## 6 Correlation between Atrial Electrical Disturbances and Atrial Acute Myocardial Infarction. An Autopsy Study of 100 Cases

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**Background:** Atrial involvement in acute myocardial infarction (AMI) usually develops in absence of relevant clinical manifestations. However, it gains significance when AMI causes ventricle insufficiency, as in these circumstances the heart output depends mainly on atrium muscle contraction. A clinicopathological study correlating the conducting system disorders with atrial AMIs is still lacking.

**Design:** Two whole slices of the atrial myocardium (above the atrioventricular sinus and 1 cm above) and the conducting system, including perinodal zones, were microscopically analyzed in 100 hearts. Data were correlated with electrocardiograms in all cases.

**Results:** Significant disturbances in the atrial rhythm were detected in 67 cases, 41 of them (61.2%) showing atrio-ventricular block (AVB). Atrial AMI was detected in 56 cases (83.5%). A positive correlation between AVB and acute lesions in the atrial muscle or in the conducting system was found. Diffuse atrial myocardial infarction was detected in 97.5% (40/41) of cases presenting AVB. However, the atrio-ventricular node was specifically damaged only in 31.7% (13/41) and perinodal muscle fibers in 73.1% (30/41) of them.

**Conclusions:** Atrial AMI leads to significant supraventricular rhythm disturbances. Ischemic damage of the atrio-ventricular node is not frequent in AVB. Ischemic lesions of perinodal muscle fibers are frequently involved in AVB. Diffuse atrial muscle infarction is the most frequent histologic finding in AVB.

## 7 Serum Troponin Levels To Evaluate Myocardial Infarction Size in Human Beings: Comparison with CK-MB and Necropsy Findings

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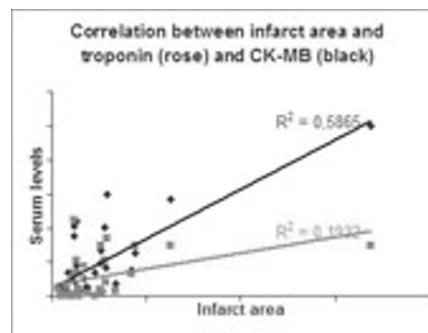
**Background:** The elevation of serum levels of troponin is increasingly used as a diagnostic criterion of acute myocardial infarction. However, differently from heart-related

fraction of creatino-kinase (CK-MB), there is no article showing the relationship between those levels and the size of the area of necrosis in human beings. So we analyzed the size of infarction in necropsy hearts, comparing with the troponin and CK-MB serum levels.

**Design: PATIENTS AND METHODS:** The areas of 34 myocardial infarcts and the total areas of ventricles were measured in 31 necropsy hearts. Twenty-two patients were male. Age of patients ranged from 50 to 86 (mean 68.81) years. In each heart, 1-cm-thick transversal sections of the ventricles were cut from the base to the apex and circumscribed in a computer-linked image analysis system. Only cases with macroscopically visible infarctions were included. The slices had also been weighted. The weight of the necrotic area was calculated by multiplying the total weight of each slice by the ratio infarct area/total area previously measured in each of them. The correlations of both the sum of the area of myocardium infarction in all slices and the weight of the necrotic myocardium with serum highest values of CK-MB and troponin which had been quantified during life by chemiluminescence immunoassay were verified by Pearson's test; results were considered significant if  $p \leq 0.05$ .

**Results:** A good correlation coefficient was detected between infarct size and CK-MB peak ( $r=0.77, p<0.01$ ), infarct weight and CK-MB peak ( $r=0.75, p<0.01$ ) and between CK-MB and troponin highest values ( $r=0.78, p<0.01$ ); nevertheless, the correlations between troponin level and infarct size and weight, although significant, were low ( $r=0.44, p=0.02$  and  $r=0.48, p=0.02$  respectively).

**Conclusions:** It is well established that the elevation of troponin serum levels is a very good diagnostic tool for myocardial infarction. Nevertheless, differently from CK-MB, it has a poor correlation with the extension of the lesion in human beings.



## 8 "Fresh" Post-Intubation Tracheal Stenosis with Granulation Tissue: An Extremely Dangerous Lesion

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**Background:** Otolaryngologists are aware of acquired tracheal stenosis as a possible complication of cuffed endotracheal tubes being required for airway maintenance for moderate or prolonged time periods. With careful use of low-pressure cuffs in more recent decades, severe degrees of the complication are much less common than they were half-century ago. Most cases initially present many weeks after the intubation episode and, while some are quite serious, seldom does one encounter a truly acutely emergent situation.

**Design:** We briefly describe the case of a young 26-year-old man who died emergently from postintubation tracheal stenosis of relatively recent onset. The pathologic details of the abnormal tracheal tissues, together with a simple quantitative mathematical analysis of the lesion, indicate just how markedly dangerous this type of lesion can be and why it was fatal in this case.

**Results:** The process occupied the upper 3 cm of the trachea. The tissues forming the stenotic segment were not symmetrical but did involve most of the circumference within this segment forming a 3-cm sleeve of pathologic tissue. The abnormal sleeve was in an area where the mucosal epithelium had been ulcerated and replaced with a soft tissue growth composed of swollen, reddish granulation tissue. The integrity of the cartilage wall of the trachea was maintained. Immunostains for adenovirus, Herpes virus, and EBV-LMP were negative. Expansion of lesional granulation tissue was prevented in outward direction by the intact tracheal wall. With a long sleeve attached to the wall, lengthwise expansion was limited. All swelling of the granulation tissue occurred at the expense of the airway lumen. The percentage loss of luminal area increased geometrically, meaning that the loss of vital airway tended to be an ever-accelerating life threatening process.

**Conclusions:** This patient's lesion was extremely dangerous. Recognition of such a lesion rests primarily upon four considerations: first appearance of symptoms (e.g., stridor) relatively early in the post-intubation period; increase in symptoms during this early period; endoscopic and histopathologic impression of the degree of vascularity of the abnormal tissue in the airway; a long, circumferential lesion will be significantly more dangerous than others. The extent to which these parameters are present should increase concern that the patient may have a truly dangerous airway lesion. For such a patient, early consideration of laser obliteration of the granulation tissue and very close follow-up care might be life-saving.

### 9 Survey of 160 Internal Medicine and Pathology Resident Physicians on the Importance and Acquisition of Autopsies

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**Background:** The national paucity of autopsies negatively impacts physician education and quality control to an unknown degree. This study compares internal medicine and pathology resident perceptions of autopsy including: importance, procurement, technique, and the pathologist-internist interaction.

**Design:** An 84-item survey based on autopsy literature was designed with a Likert scaling system (strongly agree=5; agree=4; do not know/no opinion=3; disagree=2; strongly disagree=1) (n=55) and select/rank applicable statements (n=29) and distributed to 214 residents. Mean Likert scores and weighted select/rank averages were calculated. Significance is  $p < 0.05$  by 2-tailed Student t-test. Agreement & disagreement are considered only when 95% confidence intervals exclude 3.

**Results:** Surveys from 72% of medicine (n=118) and 84% of pathology (n=42) residents were collected. There was strong agreement (mean score >4) on the importance of autopsies for education, answering clinical questions, public health, and research. Autopsy rates are ranked inadequate (2.5). Internists are comfortable requesting autopsies (3.3), but report having insufficient guidance (2.8) and ability to answer technical questions (2.1). While not requested on all hospital deaths (2.9), internists are more likely to initiate an autopsy request (3.3) than a decedents family (2.7,  $p=0.00$ ), and worry less about institutional costs (2.2) and malpractice litigation (2.4) than pathologists believe (3.2,  $p=0.00$ ). Housestaff expressed interest in: having an instructional brochure to give families (3.9), observing an autopsy (3.5), and having increased communication (3.3) and assistance (3.4) with autopsies from pathology residents. The highest ranked reasons why autopsy consent is not requested (it is unpleasant, cause of death is known, family is upset or seems unwilling) and why families refuse (patient has suffered enough, body may be handled disrespectfully, religious/moral objections, lack information) were similar for both resident groups.

**Conclusions:** Despite their decline, the perceived importance of autopsies in medicine is still very high among internal medicine and pathology residents at a large academic center. Improving autopsy education, enhancing availability of resources and strengthening pathologist-internist interactions may serve to heighten awareness and ultimately procurement. (\*Equal contribution by authors.)

### 10 The Major Autopsy Findings in Adult Patients after Bone Marrow Transplantation

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**Background:** Hematopoietic stem cell transplantation (HSCT) is an important treatment for a variety of malignant and nonmalignant conditions. However the procedure is associated with high mortality and morbidity. The aim of this study is to characterize the major autopsy findings in HSCT recipients.

**Design:** Retrospective review of all autopsy pathology material for those patients at Wayne State University affiliated hospitals was conducted from 1995 to 2005. Determination of the major pathologic finding leading to patients demise in the first 100 days and beyond 100 days post transplant is presented.

**Results:** A total of 66 patients were found, 52 (79%) were allogeneic and 14 (21%) autologous. Death occurred at a median of 85 days post transplantation (range 2-1825 days), 36 (55%) in the first 100 days and 30 (45%) beyond that. The pulmonary complications were the most frequent and were found in 40 (60%). The most common findings in the first 100 days post transplant were diffuse alveolar damage (DAD) in 10/36 (28%) followed by acute pneumonia in 6/36 (17%) and Aspergillosis in 5/36 (14%); and after 100 days they were DAD 7/30 (23%), pneumonia 5/30 (17%), metastasis 5/30 (17%) and Aspergillosis 4/30 (13%). The most common findings in allogeneic type were DAD in 15/52 (29%), Aspergillosis in 9/52 (17%), pneumonia in 9/52 (17%) and gastrointestinal bleeding in 6/52 (12%). However, in the autologous type, the most common were metastasis in 6/14 (43%), DAD in 2/14 (14%) and pneumonia in 2/14 (14%). No cases of Aspergillosis were found in the autologous group. Other less frequent findings that were found are: systemic Candidiasis, post transplant lymphoproliferative disorder, pulmonary embolism and disseminated Cytomegalovirus infection.

**Conclusions:** Pulmonary findings in the form of DAD, pneumonia and Aspergillosis are the commonest autopsy findings. Metastasis was found to be more common in autologous as well as in the period beyond 100 days compared to allogeneic and the period before 100 days, respectively. Paying attention to these entities may help in prevention of some of these fatal cases.

### 11 Nursing Home Deaths Which Fall under the Jurisdiction of the Coroner: An 11-Year Retrospective Study

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**Background:** Twenty percent of deaths in the United States occur in nursing homes. There is limited literature on the causes and manners of these deaths, since less than 1% come to autopsy. The current study analyzed causes and manners of death in all nursing home deaths investigated by the Coroner of the County of Allegheny, Pennsylvania which has the second highest elderly population in the United States.

**Design:** All cases from nursing homes autopsied by the Allegheny County Coroner's Office from 1993 to 2004 were electronically identified from the official database. In each case the age, sex, race, marital status, manner and cause of death were extracted. Statistical analyses for the abstracted variables were performed using descriptive statistics and Chi Square analysis. The final autopsy and death investigation reports were reviewed by two of the authors (JLL and BIO).

**Results:** A total of 208 cases were identified. The age ranged between 19 and 91 years

old. Thirty-three cases were under the age of 65 (15%). Women represented 58% of cases and men 42%. 121 deaths were ruled accidental (A) (58%) and 80 natural (N) (38.5%). There were two homicides, two suicides, three undetermined. 88% were white (W), 22% African-American (AA) and 1 was Hispanic. The manner of death was significantly different between W and AA, with 92.6% of A deaths in W and 6.6% in AA ( $p < 0.1$ ). In the 40 cases of N deaths the most common autopsy findings were: arteriosclerotic cardiovascular disease (ASCVD) (n=62) and non-ASCVD (n=20), pneumonia (n=29), pulmonary embolism/deep vein thrombosis (n=7), chronic obstructive pulmonary disease (n=6), seizure disorder (n=5), and traumatic intracranial hemorrhage (n=5). In A deaths, blunt force trauma (BFT) was the single most commonly identified traumatic event with trauma to the head, neck, trunk and extremities identified in 32, 8, 2, and 7 cases, respectively. Other autopsy findings included: asphyxia (n=15), drug overdose (n=4), burns (n=3). In A deaths chronic and acute diseases were similar to those seen in N deaths.

**Conclusions:** Accidental deaths might be more common in W as compared to AA nursing home residents. Homicides and suicides are rare events in the nursing home (<2%). BFT is a major autopsy finding in accidental nursing home deaths and a root cause analysis may be helpful in developing policies and procedures to decrease the incidence of BFT.

### 12 Ophthalmic Pathology of Ataxia-Telangiectasia: Description of the First Case

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**Background:** Ataxia-telangiectasia (AT) is an autosomal recessive disease characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia and increased susceptibility to infections and malignancy. Although conjunctival telangiectasias are one of the characteristic features of AT, there are very few reports of AT in the ophthalmology literature, and no description of the ocular pathology. In this work, we present the first report of the ocular pathology of AT.

**Design:** The index patient presented at age 2 years with failure to thrive, developmental delay, recurrent sinopulmonary infections and unsteady gait. At age 3, numerous telangiectasias were noted on the bulbar conjunctiva, face, external ear, and hard palate. Laboratory studies showed elevated serum alpha-fetoprotein. The presence of early onset ataxia, oculocutaneous telangiectasia, and elevated serum alpha-fetoprotein allowed the diagnosis of AT. The patient continued to suffer from frequent sinopulmonary infections. By age 8, he was confined to a wheelchair because of severe ataxia. At age 9, he suddenly developed headache, nausea, vomiting and left sided hemiparesis. Brain CT-scan showed a large right cerebral hemorrhage. Resection of large cerebral arteriovenous malformation was performed with dismal postoperative course and death. Permission was granted for a full autopsy.

**Results:** Microscopic examination of the eyes revealed ectatic thin-walled vessels in the substantia propria underlying the conjunctival epithelium. Within the telangiectatic vessels, endothelial cells with bizarre nuclei and focal acute perivascular hemorrhage were noted. There was also bizarre enlargement of cell nuclei to 2-5 times normal size (amphicytes) in the conjunctival epithelium and substantia propria near the limbus. In addition, bilateral dilatation of the choroidal vessels (choroidal telangiectasias) was seen. These lesions primarily involved the posterior poles and had no discrete margins.

**Conclusions:** We present a case of AT with the following ophthalmologic findings: - Bilateral diffuse choroidal telangiectasias - Bilateral conjunctival telangiectasias - Bilateral nuclear atypia of conjunctival epithelium, endothelium and stromal cells. Choroidal telangiectasias have never been recognized in AT by ophthalmologic examination. The failure to recognize them clinically may be because they often are extremely difficult to recognize by funduscopy, just like choroidal hemangiomas, or they may be a rare manifestation of AT, or finally, they may be present only in specific subtypes of AT.

### 13 Sudden and Unexpected Death Due to Extranodal Anaplastic Large Cell Lymphoma: An Autopsy Series with Clinical Correlation

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**Background:** Anaplastic large cell lymphoma (ALCL) is clinically and pathologically heterogeneous subset of T-cell lymphoma, leading to some difficulty in clinical and morphological diagnosis. Unusual clinical presentation is particularly associated with the extranodal variants of ALCLs often delaying correct diagnosis and adequate treatment. Here, we describe four cases of clinically unrecognized ALCLs with rapid progression and unexplained death. Gross, morphologic and immunohistochemical findings are discussed.

**Design:** Four case of ALCL were identified in autopsy files in the period from 2000-2005. Clinical charts as well as autopsy findings were reviewed. Microscopic H&E slides as well as immunohistochemical stains were evaluated.

**Results:** Four autopsy cases of ALCL were identified with two male and two female patients (average age of 36.3, ranging from 9-57 years) with hospital stay of less than 7 days. All of the cases were clinically unrecognized as lymphoma. The main clinical findings were those of fatigue (all four cases), asthmatic attack (case 1), shortness of breath (case 2), weight loss with metabolic acidosis (case 3) and fulminant liver failure (case 4). The primary extranodal sites were mediastinum, pericardium, spleen, and liver (case 1-4 respectively). Gross tumor masses were identified on autopsy in cases 1-3 (mediastinum, pericardium and spleen) while liver in case 4 did not show gross lesion. Lymphoma was grossly suspected in cases 1 and 4 while pericardial mass grossly appeared as metastatic carcinoma. All cases were positive for CD3 and CD30 and were negative for LCA, cytokeratin, vimentin, desmin, HMB-45, S-100, ALK-1 and CD20.

**Conclusions:** Clinical challenge in all four of presented cases was in making a clinical suspicion of lymphoma in rapidly progressing disease without clinical

lymphadenopathy in which clinical signs were just reflecting the failure of the affected organ. Absence of gross tumor mass can even hinder the final autopsy diagnosis. Morphological heterogeneity, similarity with other non-lymphoid poorly differentiated neoplasms, and negative initial immunohistochemical panel can further obscure final diagnosis. Therefore, in cases with sudden and unexplained death presenting with plethora of unusual metabolic and clinical findings, a meticulous search for possible extranodal lesions with extensive immunohistochemical workup including CD30, T-cell markers and ALK-1 is recommended.

#### 14 Qualitative and Quantitative Immunohistochemical Analysis of Splenic Pathology in Pseudomonas Aeruginosa Sepsis (PAS)

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**Background:** Immunosuppression is known to play an important role in many diseases. However, the host response in sepsis is poorly understood. Recent literature suggests that an impaired host response may be important in sepsis. This impaired ability to fight pathogens may contribute to the sepsis-associated mortality. This study was undertaken to assess splenic pathology and host immune status in PAS.

**Design:** Pathology archival material from 24 cases of pre-mortem PAS between 1977-2003 were retrieved. A control group of 15 cases who died of non-infectious etiology were also evaluated. Slides were examined in a blinded fashion by two pathologists. Splenic white pulp was characterized as hypoplastic/depleted, early activated and evolving activated. Spleen sections were also stained with kappa, lambda, CD4 and CD8. The average number of CD4, CD8 and plasma cells per 10 consecutive high power fields (HPF) was estimated at 400X magnification.

**Results:** Thirty-eight of 39 (97.4%) patients were males with a mean age of 66.3yrs (range 38-89) amongst the PAS group and 75.2 yrs (range 60-89) in the control group. The weight of the spleens ranged from 90 - 1000gm (mean 351) amongst the cases and 60-600gm (mean 212.7) in the control group. The total white counts were similar in the two groups and range from 2,100 - 30,000/mm<sup>3</sup> (mean 9,270) amongst the cases and 3,900-30,000/mm<sup>3</sup> (mean 14,535) in the controls. (p=0.1057). Histologically, the spleen showed hypoplastic /depleted white pulp in 10(41.7%) of PAS cases and none of the controls (p=0.0005). PAS cases showed a marked reduction in CD4 positive helper T-cells with an average of 115/10HPF as compared with 492/10 HPF for the controls, (p=0.0004). The CD4: CD8 ratio was reversed in the PAS group with average CD8 counts/10HPF of 309 and 137 for the control group. (p=0.03) The total number of plasma cells in the two groups showed no statistically significant relationship with the clinical picture.

**Conclusions:** PAS shows statistically significant qualitative and quantitative differences in the spleen. PAS seems to be more often associated with hypoplastic /depleted white pulp. Moreover there is a statistically significant reduction in the number of CD4 helper T cells with reversal of the CD4: CD8 ratio. The findings seem to support the notion that immunosuppression may play a role in the pathophysiology of PAS.

#### 15 The Vitreous Proteome: An Autopsy Study

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**Background:** The vitreous fluid occupies approximately 80% of the volume of the eye, yet little is known about the composition of the vitreous in normal states or systemic disease processes. Understanding the vitreous proteome and how it changes with disease may aid in treatment and diagnosis of ocular and retinal diseases. The vitreous fluid is relatively stable after death, making it an ideal fluid to study after death. Postmortem proteomic vitreous analysis may provide a window into the pre-mortem disease state. Albumin and immunoglobulin account for more than 80% of whole vitreous proteins. We have recently determined that such carrier proteins may sequester and amplify low abundance proteins emanating from diseased tissues. We have developed a method to elute and identify them by mass spectrometry. In this proof-of-concept study, we applied this technique to vitreous samples obtained at autopsy in a research hospital.

**Design:** At autopsy, approximately 5-10cc of vitreous was collected from each eye. Ten separate autopsy samples were procured. The samples were stored at -80 degrees until the analysis could be performed. Isolation of vitreous proteins and peptide fragments was performed using solid phase albumin affinity capture under non-denaturing conditions. The captured proteins and peptides were subsequently separated by gel electrophoresis and subjected to trypsin digestion and iterative analyses by microcapillary liquid chromatography-tandem mass spectrometry.

**Results:** Multiple peptide signatures from the following proteins were found in post-mortem vitreous samples from more than one autopsy case. Proteins previously known to be present in ocular structures as well as non-ocular proteins were identified.

**Conclusions:** This pilot study successfully demonstrated the ability to identify post-mortem vitreous proteins and their relative abundance. By better defining the post-mortem vitreous proteome, we hope to find links to pre-mortem disease.

Selected post-mortem vitreous proteins

immunoglobulins	Osteopontin precursor
interleukin precursor	Neural cadherin precursor
PROSAAS	Interphotoreceptor retinoid-binding protein precursor
Triadin	Wnt inhibitory factor
S-arrestin	Von Ebner gland protein precursor
Opticin	Beta Crystallin B
Retinoschisin	Kidney specific Membrane protein NX-17
Retinoic acid receptor Responder Protein	MutS protein homolog 4
Cofilin	Dickkopf related protein-3

#### 16 Candida Infection of Lower Gastrointestinal Tract: Myth or Reality?

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**Background:** Mycetes, predominantly of the genera *Candida*, exist as habitual saprophytes in the digestive tract of healthy immunocompetent individuals. Therefore the etiological significance of gastrointestinal candida colonization continues to be controversial. *Candida* infection of the alimentary canal usually occurs in the oral cavity, oropharynx and esophagus; and is infrequently documented as credible cause of pathology in the stomach and intestines.

**Design:** In this study, we reviewed the computerized autopsy database of our institution from 1993-2005 for all cases in which candidiasis was documented at autopsy. In all, 161 cases were retrieved. These were analyzed further for cases of candidiasis involving the stomach and/or the intestines with evidence of tissue invasion. Those cases were then analyzed for patients' demographics, underlying and/or predisposing disease condition(s) and the organs involved by *Candida* infection.

**Results:** 22 of the 161 cases of *Candida* infection documented at autopsy involved the stomach and/or the intestines (i.e. lower gastrointestinal tract) and occurred in patients aged 35-83 years with a male to female ratio of 9:2. 13 of the patients were caucasians, 6 African American (blacks) and 3 hispanics. 20 of the 22 patients with lower gastrointestinal candidiasis had associated immunocompromised status due to diseases such as AIDS, cancer and organ transplant-associated immunosuppression; and 19 of them occurred in a setting of disseminated infection with associated involvement of other organs (such as lungs, kidneys, brain and bone marrow). The stomach was involved in 16 of 22 cases (73%); the small intestine in 9 cases (41%) and the large intestine also in 9 cases (41%). 7 of the 16 cases with gastric candidiasis had associated oral and/or esophageal candidiasis and 7 of the 16 cases (44%) with gastric candidiasis also had associated intestinal involvement. 6 of the 9 cases (67%) with small intestinal candidiasis has associated colonic involvement.

**Conclusions:** Clinically significant *Candida* infection of the lower gastrointestinal tract does occur and usually affect immunocompromised patients but can also occur (though infrequently) in healthy patients too. The stomach and the intestines are involved in 14% (22/161) of *Candida* infection documented at autopsy. Gastric and intestinal candidiasis are more common in male patients, tend to involve multiple segments of the gastrointestinal tract and usually occur as part of disseminated candidiasis.

#### 17 Intramyocardial Vascular Amyloid Deposition in Patients with Autopsy-Proven Cardiac Amyloidosis

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**Background:** Cardiac amyloidosis is defined by the histological presence of amorphous proteinaceous material, specifically insoluble fibrillar proteins, around myocytes and within or around intramyocardial vessels. However, the literature is unclear as to the frequency and degree of vascular involvement among the various types of amyloidosis, specifically the senile type. The purpose of this study was to determine the extent of intramyocardial vascular involvement in patients with autopsy-proven cardiac amyloidosis.

**Design:** The autopsy files at our institution from 1981 to present were reviewed to identify individuals with the postmortem finding of cardiac amyloidosis. A total of 20 cases with confirmed cardiac amyloid by Congo red staining and typical apple-green birefringence under polarized light were included. Each case was classified into a particular amyloid syndrome (senile systemic amyloidosis [SSA], n=7; primary/myeloma associated [AL], n=11; secondary, n=1; and familial, n=1) according to careful review of hospital records and files.

**Results:** Histopathologic review of available heart sections revealed intramyocardial vascular involvement in all patients with AL amyloidosis and in 6 of 7 patients with SSA. In the AL amyloidosis group, the vast majority of patients (10 of 11) demonstrated transmural to focally transmural vascular involvement with thickening of the media and narrowing of the vessel lumens. In contrast, in the patients with SSA, the vessel thickness or lumen size was not affected by the amyloid deposition, as it was concentrated largely in the adventitia and external media.

**Conclusions:** The presence of cardiac involvement by amyloid has been determined to be the most important factor guiding prognosis in patients with amyloidosis. Previous reports have shown that SSA results in slowly progressive heart failure whereas AL amyloidosis produces rapid progression of heart failure, possibly attributable to the presence of a toxic component due to the circulating monoclonal light chain. This study shows that there is considerable intramyocardial vascular involvement in both AL amyloidosis and SSA, which differs from the frequencies suggested in the literature. However the degree of vascular involvement and media expansion with subsequent narrowing of the lumen is much greater in AL amyloidosis than SSA, which also may explain the variation in progression of heart failure in these two groups. Whether the two vascular patterns reflect different pathogenic mechanisms of amyloid deposition has yet to be elucidated.

#### 18 Myocardial Interstitial Collagen Is Increased in Morbidly Obese Patients

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**Background:** Congestive heart failure is a common feature in obese patients. In obesity, excess adipose accumulation leads to increased blood volume and cardiac output. This in turn leads to left and possibly right ventricular hypertrophy and dilatation. Such patients may develop diastolic and systolic ventricular failure. Several studies indicate that the increased heart weight is not only due to hypertrophy of myocardial fibers and but also growth of myocardial fibroblasts and collagen leading to abnormal thickness and density of the collagen matrix. The aim of this study is to evaluate the degree of reactive interstitial fibrosis in the myocardial matrix of morbidly obese patients.

**Design:** Twelve morbidly obese patients (defined as patients with BMI or ≥40 kg/m<sup>2</sup>)

were selected from the autopsy files. The heart weights were collected; five micron, paraffin-embedded sections of the left ventricle were stained with Sirius Red F3BA for collagen. Multiple areas from each slide were digitized and interstitial collagen quantified using Image Pro Plus software. Collagen volume fraction was calculated and compared to collagen volume fraction from five control patients (BMI  $\leq$  25 kg/m<sup>2</sup>).

**Results:** The ages of the patients ranged from 19 to 76 (mean 46) for the morbidly obese group and 34 to 69 (mean 56) for the control group. The BMI of the obese patients ranged from 40 to 80 kg/m<sup>2</sup> (mean of 51), and the control group ranged from 23 to 25 kg/m<sup>2</sup> (mean 24). History of hypertension was present in five, absent in four and not known in three obese patients. One control patient had hypertension. Heart weight was not significantly higher in the morbidly obese group compared to controls (370  $\pm$  38 versus 354  $\pm$  31,  $p = 0.79$ , respectively). Collagen volume fraction was significantly increased in the morbidly obese patients (1.6%  $\pm$  0.22) compared to lean controls (0.6%  $\pm$  0.04),  $p < 0.05$ .

**Conclusions:** Morbid obesity stimulates cardiac interstitial collagen production. These results suggest that collagen production may contribute to the high risk of cardiac failure, especially diastolic failure, found in morbid obesity.

### 19 Discrepant Major Diagnosis and Unexpected Additional Diagnoses Found at Autopsy: A Comparison of University, Community, and Private Autopsy Practices

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**Background:** Recent studies continue to demonstrate a high disparity rate between clinical and autopsy diagnoses. Few have compared different institutional settings.

**Design:** We retrospectively reviewed consecutive adult autopsy results from three settings from 2002-2005: University hospital (n=86, patient age 59  $\pm$  17 years, 40% women, 41% Black); community hospital (n=103, patient age 61  $\pm$  15 years, 53% women, 39% Black); and private commissioned autopsies (n=55, patient age 68  $\pm$  15 years 53% women, 33% Black). The community and private autopsies were all performed by the same prosector. Major discrepancies (autopsy findings refuting accuracy of cause of death per death certificate) and major additional findings (potentially affecting patient care but not cause of death) were determined prospectively.

**Results:** The rate of major discrepancies was 8% (University), 19% (community) and 31% (private). The rate of additional major findings was 27% (University), 36% (community) and 51% (private). The largest group of major discrepancies in the combined private and community setting was undiagnosed pulmonary embolus attributed to coronary disease (40%), followed by undiagnosed infection (14%), ruptured aneurysm (14%) and undiagnosed neoplasm (11%). The largest group of major discrepancies in the University setting was undiagnosed coronary artery disease (43%). Undiagnosed infections included peritonitis (2), meningitis (1), miliary tuberculosis (1), and endocarditis (1). Undiagnosed malignancies included disseminated lymphoma (1), small cell carcinoma of lung (1), urothelial carcinoma (1); meningeal melanoma (1), and biliary carcinoma (1). By univariate analysis, discrepant findings were associated inversely with length of hospital stay ( $p < .01$ ) and private ( $p < .001$ ) and community ( $p < .01$ ) settings. By multivariate analysis, only private setting ( $p = .02$ ) correlated (inversely) with rate of discrepant results.

**Conclusions:** We conclude that unexpected findings are not uncommon in autopsy preformed currently, especially with short hospital stay and requested privately by family. The single largest misdiagnosis remains pulmonary embolus attributed to coronary artery disease.

## Bone & Soft Tissue

### 20 Genomic Gains of COL1A1-PDGFB Copies Occur in Fibrosarcomatous Transformation of Dermatofibrosarcoma Protuberans

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**Background:** Dermatofibrosarcoma protuberans (DFSP) is a superficial low grade sarcoma that rarely evolves into a higher grade fibrosarcoma. DFSP is genetically characterized by the unbalanced chromosomal t(17;22)(q21;q13), usually in the form of a supernumerary ring chromosome. The product of this chromosomal translocation is the chimeric gene COL1A1-PDGFB, which is amplified at low levels in the supernumerary ring chromosome. The aims of this study were to evaluate (1) whether additional amplification of this fusion gene occurs during the clonal evolution of DFSP into fibrosarcomatous DFSP and (2) whether there is a difference between the number of genomic copies of COL1A1-PDGFB between classic DFSP and DFSP areas associated with fibrosarcomatous DFSP.

**Design:** Ten cases of fibrosarcomatous DFSP with both DFSP and fibrosarcomatous areas and 10 cases of classic DFSP were studied. Genomic copies of COL1A1-PDGFB were evaluated by fluorescence in situ hybridization (FISH) using a custom designed probe for the PDGFB locus on 4  $\mu$ m thick paraffin-embedded tissue sections. Approximately 500-1000 cells were independently scored in both DFSP and fibrosarcomatous areas in each tumor.

**Results:** Additional gains of COL1A1-PDGFB locus signals were observed in 6 (of 10) fibrosarcomatous DFSP in the fibrosarcomatous areas (2-7 gene copies, median 4.2) when compared to the classic DFSP areas (2-3 gene copies, median 2.2). Four fibrosarcomatous DFSP did not show additional genomic gains of COL1A1-PDGFB between the two areas. No difference in the copy number of COL1A1-PDGFB fusion gene was observed between classic DFSP and DFSP areas of fibrosarcomatous DFSP (2-3 gene copies in each).

**Conclusions:** Additional genomic gains of COL1A1-PDGFB fusion gene is an oncogenic mechanism that can occur in the clonal evolution of a subset of DFSP into

fibrosarcomatous DFSP. Overall COL1A1-PDGFB fusion gene copy number in the classic DFSP areas does not seem to be a major predisposing mechanism for fibrosarcomatous transformation.

### 21 EWS-CREB1: A Recurrent Variant Fusion in Clear Cell Sarcoma Associated with Gastrointestinal Location and Absence of Melanocytic Differentiation

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**Background:** Clear cell sarcoma (CCS) usually arises in the lower extremities of young adults and is typically associated with a t(12;22) that results in the fusion of EWS with ATF1, a gene encoding a member of the CREB family of transcription factors. CCS arising in the gastrointestinal (GI) tract is extremely rare and its pathologic and molecular features are not well defined.

**Design:** In the course of testing a CCS from the colon of an 81 year old woman for the EWS-ATF1 fusion by reverse transcriptase PCR (RT-PCR), we detected a novel variant fusion of EWS to CREB1, a gene at 2q32 encoding another CREB family member highly related to ATF1. We then studied additional cases with similar features for EWS-CREB1.

**Results:** We subsequently identified two additional GI CCS with the EWS-CREB1 fusion by RT-PCR, both arising in the small bowel, both in 42 year old women. In 2/2 cases tested, EWS gene rearrangement was also confirmed by FISH and the EWS-CREB1 genomic junction fragments were isolated by long range DNA PCR. Morphologically, all 3 lesions had a solid, nested, or pseudopapillary growth pattern, with an epithelioid and uniform cytology. No melanin pigmentation was noted. By immunohistochemistry (IHC), there was strong and diffuse S100 protein reactivity, while all melanocytic markers and CD117 were negative. Neural markers, such as NSE, CD56 and synaptophysin were positive. Ultrastructurally, electrondense granules were identified in 2/2 cases but they lacked the diagnostic features of melanosomes. Finally, RT-PCR for the melanocyte-specific transcript of MITF showed only weak expression in 1/3 cases. Comparison of these 3 cases to EWS-ATF1-positive GI CCS (previously published and additional unpublished cases from our institution) suggested that GI CCS show less melanocytic differentiation regardless of the fusion type.

**Conclusions:** The recurrent variant fusion EWS-CREB1, representing a t(2;22)(q32;q12), may define a novel subset of CCS that occurs preferentially in the GI tract and shows little or no melanocytic differentiation.

### 22 Malignant Vascular Tumors of Bone: A Clinicopathologic and Radiographic Study of 78 Cases

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**Background:** We reviewed 78 cases of malignant vascular tumors collected at the Rizzoli Institute in order to better understand the pathologic features and how they correlate with biologic behavior.

**Design:** Of 155 cases coded as malignant vascular tumors, 78 met the criteria for low-grade hemangioendothelioma or high-grade angiosarcoma. Epithelioid hemangioendothelioma was excluded. Histologically, at least focal vasoformative growth pattern was required for inclusion. Tumors were graded on a scale of 1-3 based on the extent of cytologic atypia. Radiographs were available for review on 55 cases. Data on treatment and follow-up was available on 59 pts.

**Results:** 52 were males and 26 females. Bones involved were: long bones 40, small bones of foot or hand 3, vertebra 5, and flat bones (pelvis, sacrum, rib) 13. 17 pts had radiographic evidence of multicentric disease. Radiographically, a well margined rim was seen in 16 cases (15 were gr 1 or 2). 39 had an aggressive, purely lytic radiographic appearance with cortical disruption (15 = gr 1 or 2; 24 = gr 3). Histologically, lower grade tumors were more vasoformative than higher grade tumors. Tumor cells were round to oval shaped with occasional spindling in solid areas. Gr 1 tumors had minimal cytologic atypia. Nuclei in gr 2 tumors were generally uniform, but larger and with moderate hyperchromatism. Gr 3 tumors contained prominent nuclear pleomorphism. Results of grading: gr 1=20; gr 2=22; gr 3=36. Surgical treatment included: 16 curettage (gr 1=9; gr 2=2; gr 3=5); 16 wide resection (gr 1=5; gr 2=6; gr 3=5); 13 amputation (gr 1=0; gr 2=4; gr 3=9). 10 pts had a biopsy followed by radiation (gr 1=2; gr 2=2; gr 3=6). Follow-up information (59 pts) ranged from 1 to 216 mos; ave 46 mos. Five died of unrelated causes; 27 were alive w/o disease and 27 DOD (gr 1=0; gr 2=6; gr 3=21). One pt died of a post radiation sarcoma and another is alive with stable lung metastases. Treatment of pts who DOD included: biopsy with radiation: 8 (gr 2=2; gr 3=6); curettage: 5 (all gr 3); wide margin: 6 (gr 2=2; gr 3=4); amputation: 8 (gr 2=2; gr 3=6).

**Conclusions:** The biologic behavior of malignant vascular tumors of bone is related to the histologic grade. Gr 1 tumors behave in a relatively benign fashion. All of the 16 gr 1 tumors in this series are alive following conservative treatment. Gr 3 tumors are highly aggressive; 21 (of 25) with treatment and follow-up information DOD. Gr 2 tumors show histologic features and biologic behavior in-between gr 1 and gr 3 tumors; 6 (of 16) DOD.

### 23 Immunohistochemistry and FISH on Tissue Microarrays in the Evaluation of Inflammatory Myofibroblastic Tumor

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**Background:** Various gene fusions involving the anaplastic lymphoma kinase (ALK) gene at chromosome 2p23 have been described in inflammatory myofibroblastic tumor (IMT), suggesting a neoplastic etiology. The ALK rearrangement is reportedly more common in children; there are only rare IMTs in adults with genetic information. This study represents the largest series of lesions designated as IMT on morphologic grounds, with comparative ALK IHC and FISH analysis.